Effect of Captopril and Enalapril on Endothelial Function in Hypertensive Patients

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Abstract

Endothelium-dependent vasodilation is impaired in patients with essential hypertension. The objective of this study was to determine whether long-term treatment with angiotensin-converting enzyme inhibitors improves endothelium-dependent vasodilation in forearm resistance vessels of patients with hypertension. Furthermore, since tissue thiols may be relevant to nitric oxide-mediated vasodilation, we queried whether an angiotensin-converting enzyme inhibitor with a sulfhydryl group preferentially augments endothelium-dependent vasodilation in these individuals. The study included 24 patients with essential hypertension (mean age, 45±2 years) and 20 normotensive subjects (mean age, 47±1 years). Methacholine chloride (0.3 to 10 μg/min) was infused via the brachial artery to assess endothelium-dependent vasodilation in forearm resistance vessels. Nitroglycerin (1 to 30 μg/min) was administered to evaluate endothelium-independent vasodilation. Forearm blood flow was determined by venous occlusion strain-gauge plethysmography. Forearm vascular function studies were performed in hypertensive patients before and 7 to 8 weeks after randomization to either captopril or enalapril, angiotensin-converting enzyme inhibitors with and without a sulfhydryl moiety, respectively. Normotensive subjects were studied on only one occasion. Before treatment, the forearm vasodilative response to methacholine was attenuated in hypertensive compared with normotensive subjects (P<0.01). The effects of nitroglycerin on forearm blood flow did not differ significantly between the two groups. Both captopril and enalapril reduced mean blood pressure in the hypertensive subjects (12±2 versus 15±3 mm Hg, respectively; P=NS). The forearm vasodilative response to methacholine was the same during the placebo and captopril treatment periods (P=NS) and also during placebo and enalapril treatment periods (P=NS). Even when combining both treatment groups (captopril and enalapril), no significant difference in the response to methacholine was found between placebo and drug treatment periods. It is concluded that endothelium-dependent vasodilation is abnormal in forearm resistance vessels in patients with essential hypertension, thus confirming observations made previously by others. The new finding is that antihypertensive therapy for up to 7 to 8 weeks with an angiotensin-converting enzyme inhibitor does not improve endothelium-dependent vasodilation in hypertensive humans, regardless of whether or not a sulfhydryl group is present.

Key Words • endothelium-derived relaxing factor • angiotensin-converting enzyme inhibitors • captopril • enalapril • hypertension, essential • forearm • blood flow

The endothelium synthesizes a variety of vasoactive substances that regulate vascular tone, including the endothelium-derived relaxing factor (EDRF) nitric oxide.1 2 It is well established that endothelium-dependent vasodilation is impaired in conduit and resistance vessels of experimental models of hypertension and in patients with essential hypertension.3 12 This has led some to speculate that abnormalities in endothelium-dependent vasodilation may contribute to the pathogenesis of hypertension by offsetting the balance between vasoconstrictor and vasodilator forces on vascular tone,13 15 Others have implied that abnormalities in endothelial function occur after hypertension develops.16 20 Thus, reduced EDRF activity would be a consequence rather than a cause of hypertension. In either case, reduced endothelial release of EDRF/nitric oxide could not only exacerbate hypertension but perhaps contribute further to vascular injury.

Several groups of investigators have sought to determine whether antihypertensive treatment restores endothelium-dependent vasodilation in patients with essential hypertension. Panza et al13 reported that long-term treatment with antihypertensive therapy did not improve normal endothelium-dependent vasodilation in forearm resistance vessels of patients with hypertension. Hidoka et al,21 however, recently reported that administration of a single dose of the angiotensin-converting enzyme (ACE) inhibitor captopril improved endothelium-dependent vasodilation in hypertensive subjects. Supporting the latter findings are studies in vessels obtained from experimental models of hypertension. Clozel et al22 reported that the ACE inhibitors cilazapril and captopril, but not hydralazine, improved endothelium-dependent relaxation in aortic rings of spontaneously hypertensive rats. One explanation for the disparate findings is that ACE inhibitors, in contrast to other antihypertensive medications, preferentially affect endothelium-dependent vasodilation. Several investigators have suggested that ACE inhibitors increase the concentration of bradykinin, a known stimulus for EDRF release, thereby promoting endothelium-dependent vasodilation.23 24 Moreover, tissue thiols are relevant to nitric oxide-mediated vasodilation, raising the possibility that an ACE inhibitor with a sulfhydryl moiety may enhance endothelium-dependent vasodila-
tion by inducing formation of S-nitrosothiol adducts to activate guanylate cyclase.25-27

Accordingly, the objectives of this study were (1) to determine whether treatment with ACE inhibitors improves endothelium-dependent vasodilation in forearm resistance vessels of patients with hypertension and (2) to determine whether an ACE inhibitor with a sulfhydryl group preferentially improves endothelium-dependent vasodilation in these individuals.

Methods

Subjects

The subject population in this study included 24 patients with essential hypertension (18 men, 6 women; age range, 26 to 67 years; mean ± SE, 45 ± 2 years). The mean blood pressure in the untreated hypertensive subjects was 109 ± 3 mm Hg. The duration of hypertension ranged from 1 to 25 years (mean, 8 ± 1 years). None of the patients had clinical evidence of atherosclerosis. This was determined by the absence of symptoms of angina, claudication, or cerebrovascular ischemia or any physical evidence of arterial occlusive disease, as would be suggested by decreased pulses, asymmetrical blood pressure, or bruits. The study included 20 normotensive subjects (15 men, 7 women; age range, 35 to 60 years; mean, 47 ± 1 years). The ages of the patients with hypertension and the normotensive subjects were not significantly different. Normalcy was determined by careful history, physical examination, and laboratory analysis to exclude individuals with hematologic, renal, or hepatic dysfunction. The mean blood pressure in the normotensive subjects was 79 ± 2 mm Hg. This study was approved by the Human Research Committee of Brigham and Women’s Hospital, and each subject gave written informed consent.

Experimental Protocol

After an initial screening period to confirm eligibility requirements, hypertensive patients were withdrawn from all antihypertensive medications and followed for 2 weeks. If blood pressure did not increase to values exceeding 180/120 mm Hg, patients were allowed to continue their participation and were administered placebo, in a single-blind manner, for 4 weeks. Forearm vascular function studies, described below, were then performed. Thereafter, patients were randomized in a double-blind manner to treatment with one of two drugs: captopril, an ACE inhibitor with a sulfhydryl moiety; or enalapril, an ACE inhibitor that does not have a sulfhydryl group. Over the next 3 to 4 weeks, the dose of each drug was titrated to achieve normotension, ie, a blood pressure less than 140/90 mm Hg, or a maximal dose of each drug, which was 75 mg PO twice daily for captopril and 15 mg PO twice daily for enalapril. After 4 more weeks of treatment at a stable dose of the respective ACE inhibitor, the forearm vascular function studies were repeated. Normotensive subjects were studied on only one occasion.

Vascular Function Studies

Each subject was studied in a 23°C temperature-controlled room in the postabsorptive state. Alcohol, caffeine, and cigarettes were all prohibited within 12 hours of the study. Under local anesthesia and sterile conditions, a polyethylene catheter was inserted into a brachial artery of each subject for determination of blood pressure and for infusion of drugs. The vascular research laboratory was quiet, and lights were dimmed. All subjects rested at least 30 minutes after catheter placement to establish a stable baseline before data collection.

During the control period, measurements of forearm blood flow and blood pressure were repeated every 10 minutes until stable. Dextrose 5% was infused intra-arterially at a rate of 0.4 mL/min during the control period. To determine the maximal vasodilative potential of the resistance vessels, forearm blood flow was measured in the basal state and during peak reactive hyperemia after 5 minutes of an ischemic stimulus. Ischemia was induced by inflation of a sphygmomanometric cuff on the upper arm to suprasystolic pressure. Measurements of peak reactive hyperemic blood flow were made within 10 seconds of cuff deflation. Abnormalities in reactive hyperemic blood flow often imply structural problems in the resistance vessels, preventing maximal vasodilation. Forearm blood flow measurements were repeated until basal conditions were reestablished.

The protocol used to examine forearm vascular reactivity in patients with hypertension and normal subjects has been reported previously.28 To specifically assess endothelium-dependent vasodilation, methacholine chloride (a congener of acetylcholine) was administered via the brachial artery. Forearm blood flow was measured during infusion of methacholine chloride at concentrations of 0.3, 1, 3, and 10 μg/min, each for 3 minutes, delivered at a rate of 0.4 mL/min. To distinguish abnormalities in endothelial function from abnormalities of vascular smooth muscle, subjects received an intra-arterial infusion of nitroglycerin. This agent, which acts directly on vascular smooth muscle by stimulating soluble guanylate cyclase and inducing hyperpolarization, was given at doses of 1, 3, 10, and 30 μg/min, at a rate of 0.4 mL/min, each for 3 minutes. The order of administration for methacholine chloride and nitroglycerin was randomized for each subject. Basal conditions were reestablished before each intervention. The doses of each drug were chosen to achieve decreases in forearm vascular resistance without causing systemic effects. Dose-response curves were generated for each drug infusion.

Results

The pertinent hemodynamic characteristics of the hypertensive and normotensive subjects are provided in the Table. Basal forearm blood flow was significantly

Statistical Analysis

Results are presented as mean ± SE. A between-within split plot design analysis was employed to compare the response of the drug infusions between the hypertensive and normal subjects. Single-factor repeated-measures ANOVA followed by a Newman-Keuls post hoc test was used to compare the effect of each vasoactive drug in the hypertensive patients before and after randomization. Student’s t test was used to compare paired data only. Statistical significance was accepted at the 95% confidence interval at P < .05.

Results

The pertinent hemodynamic characteristics of the hypertensive and normotensive subjects are provided in the Table. Basal forearm blood flow was significantly
higher in the hypertensive subjects. Peak reactive hyperemic blood flow tended to be somewhat less in patients with hypertension than in normotensive subjects, but the difference between groups did not achieve statistical significance. Basal forearm vascular resistance was comparable between groups. Minimal forearm resistance, obtained during peak reactive hyperemia, was significantly greater in patients with hypertension than in normotensive subjects, indicating an impairment in maximal vasodilator capacity.

**Vasodilative Responses in Hypertensive Versus Normotensive Subjects**

Intra-arterial infusion of methacholine chloride caused a dose-dependent and significant increase in forearm blood flow and decrease in forearm vascular resistance in both hypertensive and normotensive subjects. In the hypertensive subjects, however, cholinergic vasodilatation was attenuated compared with normotensive subjects (Fig 1). The differences between the groups were significant at each dose of methacholine. At the highest dose of methacholine, forearm blood flow increased 414±58% in hypertensive subjects and 39.5±2.9% in normotensive subjects (P<.01). Similarly, the decrease in forearm vascular resistance was significantly less in hypertensive subjects than in normotensive subjects at doses of 0.3 μg/min (−47±5% versus −62±2%), 1.0 μg/min (−56±5% versus −73±2%), 3.0 μg/min (−66±4% versus −81±1%), and 10.0 μg/min (−74±4% versus −85±1%), respectively (all P<.01).

No changes in forearm blood flow occurred in the noninfused arm in either subject group. In addition, intra-arterial infusion of methacholine chloride caused no change in blood pressure or heart rate in either group of subjects.

Infusion of nitroglycerin also increased forearm blood flow and decreased forearm vascular resistance in hypertensive and normotensive subjects. In contrast to the attenuated response to methacholine chloride observed in the hypertensive subjects, the effects of nitroglycerin on forearm blood flow and forearm vascular resistance did not differ significantly between the two groups (Fig 2). At a dose of 30 μg/min, forearm blood flow increased 205±26% and 232±31% and forearm vascular resistance decreased −61±4% and −65±4% in hypertensive and normotensive subjects, respectively (each P=NS). No changes in forearm blood flow or forearm vascular resistance occurred in the noninfused arm of either group of subjects. Taken together, these data confirm that endothelium-dependent vasodilation is impaired in patients with essential hypertension.

**Effect of ACE Inhibition on Endothelium-Dependent Vasodilation**

Twenty-two hypertensive patients were treated with an ACE inhibitor and completed placebo and treatment forearm vascular function studies. Two patients withdrew before the second study. Each drug reduced mean blood pressure (Fig 3). Captopril decreased mean blood pressure from 109±5 mm Hg on placebo, determined at the first vascular function study, to 98±9 mm Hg, determined at the second vascular function study (P<.001). Similarly, enalapril reduced mean blood pressure from 110±4 mm Hg to 95±3 mm Hg (P<.001). There was no significant difference in the magnitude of blood pressure reduction between the two treatment groups (12±2 versus 15±3 mm Hg for captopril and enalapril, respectively). Mean blood pressure in the treated hypertensive groups remained higher than that in normotensive subjects (P<.01).

Eleven hypertensive patients were treated with captopril. Neither basal forearm blood flow (3.3±0.4 to 2.9±0.4 mL/100 mL per minute; P=NS) nor forearm vascular resistance (40±5 to 38±4 U; P=NS) changed during captopril treatment. The forearm blood flow
response to methacholine chloride was the same during the placebo and captopril treatment periods (Fig 4). At doses ranging from 0.3 to 3 μg/min, captopril tended to cause a mild augmentation in blood flow, but this did not reach statistical significance. Similarly, there was no significant difference in the forearm blood flow response to intra-arterial nitroglycerin between the placebo and captopril treatment periods (data not shown). Eleven hypertensive patients were treated with enalapril. Neither basal forearm blood flow (3.1±0.3 to 28±0.4 mL/100 mL per minute; P=NS) nor forearm vascular resistance (32±1 to 29±1 U; P=NS) changed during enalapril treatment. The forearm blood flow response curves to methacholine chloride during the placebo and enalapril treatment periods were virtually identical (Fig 5). Similarly, there was no significant difference in the forearm blood flow response to nitroglycerin between the two treatment periods (data not shown).

To ascertain further that 7 to 8 weeks of treatment with an ACE inhibitor did not substantially affect endothelium-dependent vasodilation in forearm resistance vessels, the results from both the captopril and enalapril treatment groups were combined. The design allowed us to address the issue of whether ACE inhibitors, as a class, restore endothelium-dependent vasodilation. Furthermore, the larger number of subjects increases statistical power, thus reducing the risk of a β-error. Nonetheless, even when combining both treatment groups, we found no significant difference in the forearm vasodilative response to methacholine between the placebo and drug treatment periods (Fig 6). Similarly, the forearm blood flow response to nitroglycerin during the placebo and ACE inhibitor treatment periods was comparable (Fig 7).

Discussion

The results of this study enable us to conclude that endothelium-dependent vasodilation is abnormal in forearm resistance vessels of patients with essential hypertension, thus confirming observations made previously by others.6,7,9 The principal new finding is that antihypertensive therapy with an ACE inhibitor does not improve endothelium-dependent vasodilation in hypertensive humans, regardless of whether a sulfhydryl group is present. This discussion will briefly review endothelium-dependent vasodilation in hypertension and discuss our reasoning for failing to confirm the hypothesis that ACE inhibitors improve endothelium-dependent vasodilation in patients with hypertension.

Endothelium-Dependent Vasodilation Is Abnormal in Hypertension

Most, but not all, studies in experimental models of hypertension have found that endothelium-dependent relaxation is abnormal in both conduit and resistance vessels.3,5,30 Similarly, studies in humans have shown
abnormal endothelium-dependent vasodilation in forearm resistance vessels, coronary resistance vessels, and epicardial coronary arteries. In this study the vasodilative response to the highest dose of methacholine chloride was approximately 33% less in hypertensive than in normotensive subjects, consistent with abnormal endothelium-dependent vasodilation. The vasodilative response to the endothelium-independent agent nitroglycerin was comparable between the two groups. These data not only confirm those of previous studies but demonstrate that the technique used in our laboratory is valid.

Mechanisms of Endothelial Dysfunction

We assume that abnormalities in endothelium-dependent vasodilation in human hypertension are secondary to reduced release or activity of EDRF/nitric oxide. This assumption is based on the following information. The forearm vasodilative response to cholinergic agonists is inhibited by N°-monomethyl-L-arginine, the nitric oxide synthase antagonist, and not by aspirin, indomethacin, or phenolamine. N°-monomethyl-L-arginine inhibits forearm vasodilation more in normotensive than in hypertensive subjects. In animal models of hypertension, however, the mechanism of abnormal endothelium-dependent vasodilation is less clear. It has been attributed variably to abnormalities in the EDRF/nitric oxide pathway, decreased endothelium-derived hyperpolarizing factor, or increased release of vasoconstrictor prostanoids. Different models of hypertension, vessels of interest, and agents used to induce endothelium-dependent relaxation may account, in part, for the variability among studies. One might anticipate, therefore, that endothelium-dependent responses to antihypertensive therapy may differ among animal studies per se and between animal models and patients with hypertension.

Effect of Antihypertensive Treatment

Our findings are consistent with those of Panza et al, who reported that withdrawal of antihypertensive medication did not affect endothelium-dependent vasodilation of forearm resistance vessels in patients with hypertension. Patients in that study were being treated with a variety of antihypertensive medications, and most were not taking an ACE inhibitor. Our findings are also consistent with a preliminary report by Kiowski et al, who reported that long-term treatment with the ACE inhibitor perindopril did not affect endothelium-dependent vasodilation of forearm resistance vessels of hypertensive patients. The findings, however, appear to conflict with those of Hirooka et al, who reported that administration of a single dose of captopril, but not nifedipine, improved endothelium-dependent vasodilation in forearm resistance vessels of hypertensive patients. Both drugs reduced blood pressure to a similar extent, suggesting that it was the ACE inhibitor and not simply the reduction in blood pressure that was responsible for the observation. The study by Hirooka et al differed from all other studies in humans in that the forearm vasodilative response to acetylcholine was impaired in hypertensive patients only at low doses of acetylcholine but not at the higher doses. It is noteworthy, then, that captopril had no effect on endothelium-dependent vasodilation at the highest doses of acetylcholine. Nonetheless, these findings cannot be discounted because multiple studies in experimental models of hypertension also have found that ACE inhibitors improve endothelium-dependent relaxation.

We had thought that an ACE inhibitor with a sulfhydryl moiety would be particularly likely to enhance endothelium-dependent vasodilation in hypertensive subjects. The potential of such an agent would be not only to augment endothelium-dependent vasodilation via bradykinin potentiation but also to enhance endothelium-dependent vasodilation by inducing formation of S-nitrosothiol adducts or by preventing inactivation of nitric oxide by scavenging superoxide anions. These latter properties have previously been attributed to captopril but not to enalapril. Recent preliminary studies from our laboratory, however, do not support this postulate. We found that N-acetylcysteine, a sulfhydryl donor, potentiated the vasodilator response to nitroglycerin but not methacholine chloride in forearm resistance vessels of normotensive humans subjects, suggesting that thiol is not a limiting factor for EDRF activity.

In the present study the forearm blood flow response to methacholine chloride was similar during the placebo and captopril treatment periods. It was noted, however, that captopril tended to cause a mild augmentation of blood flow at low doses of methacholine, but this did not reach statistical significance. The dose-response curves to methacholine chloride during placebo and enalapril treatment periods were virtually superimposable. Thus, neither ACE inhibitor significantly affected endothelium-dependent vasodilation in our hypertensive patients. In addition, we combined both treatment groups to increase statistical power and address the issue of whether ACE inhibitors, as a class, restore endothelium-dependent vasodilation. No significant difference in endothelium-dependent vasodilation was found between the placebo and drug treatment periods, indicating that up to 7 to 8 weeks of treatment with an ACE inhibitor does not substantially affect endothelium-dependent vasodilation in patients with hypertension.

Limitations of the Study

Negative findings suggest that the original hypothesis was not correct or that the methods used to test the hypothesis were inadequate. The variability of repeated forearm blood flow measurements during a 2-month
period may have precluded our ability to detect a small change in endothelium-dependent vasodilation during the treatment phase. It is possible that the mild, albeit statistically insignificant, improvement in endothelial function observed during captopril treatment would have become significant if a larger number of subjects had been enrolled. One might argue also that we did not treat our hypertensive patients long enough or well enough to realize a beneficial effect on endothelial function. Lüscher et al. found that antihypertensive treatment improved endothelium-dependent vasodilation in Dahl salt-sensitive rats after 2 weeks of treatment. Clozel et al. reported that 4 days of cilazapril administration improved endothelium-dependent relaxation in spontaneously hypertensive rats. Furthermore, Hirooka et al. reported their observations after only a single dose of captopril. Thus, we doubt, but cannot be certain, that endothelium-dependent vasodilation would be restored after a longer treatment period. It is also possible that the magnitude of the blood pressure reduction was insufficient to affect endothelium-dependent vasodilation. We did strive to reduce blood pressure to normotensive levels, ie, less than 140/90 mm Hg. However, the posttreatment blood pressure in our hypertensive patients still exceeded that of our normotensive control subjects. It is possible that we did not reach the threshold at which a restoration of endothelial function would have occurred. We think this unlikely since there was no overall tendency to improve endothelium-dependent relaxation during ACE inhibitor treatment in the group as a whole or in those patients with the greatest reduction in blood pressure.

In conclusion, our data confirm observations made previously by others that endothelium-dependent vasodilation is abnormal in forearm resistance vessels of patients with hypertension. The new findings are that 2 months of antihypertensive therapy with an ACE inhibitor does not improve endothelium-dependent vasodilation in these patients, regardless of whether or not a sulfhydryl group is present. It remains possible, albeit unlikely, that longer or more aggressive ACE inhibitor therapy may have favorably affected endothelium-dependent vasodilation in these individuals. Our data do not enable us to make conclusions about other antihypertensive agents. Thus, ACE inhibitors are effective antihypertensive agents with many favorable properties; however, augmentation of endothelium-derived vasodilation does not appear to be one of them.

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